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Improved pharmacokinetic properties of a polyethylene glycol-modified form of interferon-beta-1a with preserved in vitro bioactivity.

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Pepinsky RB, LePage DJ, Gill A, Chakraborty A, Vaidyanathan S, Green M, Baker DP, Whalley E, Hochman PS, Martin P.

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Interferon therapies suffer from a relatively short half-life of the products in circulation. To address this issue we investigated the effects of polyethylene glycol modification (PEGylation) on the pharmacokinetic properties of human interferon (IFN)-beta-1a. PEGylation with a linear 20-kDa PEG targeted at a single site on the N-terminal amine had no deleterious effect on its specific activity in an in vitro antiviral assay. In monkeys, PEG IFN-beta-1a treatment induced neopterin and beta2-microglobulin expression (pharmacodynamic markers of activity). Systemic clearance values in monkeys, rats, and mice decreased, respectively, from 232, 261, and 247 ml/h/kg for the unmodified IFN-beta-1a to 30.5, 19.2, and 18.7 ml/h/kg for the PEGylated form, while volume of distribution values decreased from 427, 280, and 328 ml/kg to 284, 173, and 150 ml/kg. The decreased clearance and volume of distribution resulted in higher serum antiviral activity in the PEG IFN-beta-1a-treated animals. In the rat, a more extensive set of dosing routes was investigated, including intraperitoneal, intratracheal, and oral administration. Bioavailability for the PEG IFN-beta-1a was similar to the unmodified protein for each of the extravascular routes examined. For the intraperitoneal route, bioavailability was almost 100%, whereas for the oral and intratracheal routes absorption was low (<5%). In rats, subcutaneous bioavailability was moderate (28%), whereas in monkeys it was approximately 100%. In all instances an improved pharmacokinetic profile for the PEGylated IFN-beta-1a was observed. These findings demonstrate that PEGylation greatly alters the pharmacokinetic properties of IFN-beta-1a, resulting in an increase in systemic exposure following diverse routes of administration.

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Comment in:
- Neurology. 2000 Jun 13;54(11):2034-5.

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A comparative study of the relative bioavailability of different interferon beta preparations.

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BACKGROUND: Three different recombinant interferon beta (IFNbeta) preparations are currently available for the treatment of MS, two IFNbeta-1a products (Rebif and Avonex) and one IFNbeta-1b product (Betaferon). These products differ with respect to the recommended dose, the dosage regimen, and the injection route. This study compared the relative biologic activity of these three products in vitro and in vivo. METHODS: Blood samples were collected from 237 patients with MS (170 on IFNbeta therapy and 67 control subjects receiving no therapy). Samples with neutralizing antibodies were excluded. Levels of the antiviral protein MxA and soluble vascular cell adhesion molecule-1 (sVCAM) in the four groups were measured by ELISA. In the in vitro investigation, untreated blood was incubated for 24 hours with increasing concentrations of the three IFNs from a dose of 1 IU/mL to 1000 IU/mL, after which levels of MxA were measured. RESULTS: A difference between the groups was observed in vitro, with a significant change from baseline in MxA levels being observed at 10 IU for Betaferon compared with 100 IU for Rebif and Avonex. However, this might be due to the different methods used for the determination of IU by the manufacturers. At the single-dose level there were no significant differences between IFNbeta preparations. In vivo, there were significantly different levels of MxA in the four groups. In the Betaferon group, the median value for MxA was 2.29 ng/105 peripheral blood leukocytes (PBL), compared with 1.00 ng/105 PBL for Rebif, 0.57 ng/105 PBL for Avonex, and 0.14 ng/105 PBL for the control group. Some significant differences between the groups were also apparent with respect to levels of sVCAM, which were higher with Betaferon than with Rebif. CONCLUSION: IFNbeta-1b induces higher

levels of the above markers of IFNbeta bioactivity than either of the two IFNbeta-1a preparations. Moreover, there is a less striking difference between the two IFNbeta-1a preparations in favor of subcutaneous IFNbeta-1a.

Publication Types:
- Clinical Trial

PMID: 10851362 [PubMed - indexed for MEDLINE]

1: Melanoma Res 1998 Aug;8(4):295-9 Related Articles, Books, LinkOut

Effect of natural interferon-beta on the growth of melanoma cell lines.

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Malignant melanoma is one of the fulminant skin cancers. The 5-year survival of patients with stage III (N0, N1) malignant melanoma treated with multi-agent chemoimmunotherapy, including natural interferon-beta (nIFNbeta), was found in our department to be better than that of patients treated with other forms of therapy. In order to study the effects of nIFNbeta on melanoma, the growth inhibition effect of nIFNbeta was assessed in vitro using the melanoma cell lines, MM8.1, MM28, MM33.1, Bowes and A375-2. The growth of these cell lines was inhibited by nIFNbeta. Incorporation of [3H]thymidine and [3H]uridine was also inhibited by nIFNbeta in a dose-dependent manner. Apoptosis was demonstrated using the TUNEL method in melanoma cell lines cocultured with nIFNbeta. Results showed that nIFNbeta had direct killer activity on melanoma cell lines.

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1: Pharm Res 1998 Apr;15(4):641-9

Structural and functional differences between glycosylated and non-glycosylated forms of human interferon-beta (IFN-beta).

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PURPOSE: Two recombinant IFN-beta products have been approved for the treatment of multiple sclerosis, a glycosylated form with the predicted natural amino acid sequence (IFN-beta-1a) and a non-glycosylated form that has a Met-1 deletion and a Cys-17 to Ser mutation (IFN-beta-1b). The structural basis for activity differences between IFN-beta-1a and IFN-beta-1b, is determined. METHODS: In vitro antiviral, antiproliferative and immunomodulatory assays were used to directly compare the two IFN-beta products. Size exclusion chromatography (SEC), SDS-PAGE, thermal denaturation, and X-ray crystallography were used to examine structural differences. RESULTS: IFN-beta-1a was 10 times more active than IFN-beta-1b with specific activities in a standard antiviral assay of 20 x 10(7) IU/mg for IFN-beta-1a and 2 x 10(7) IU/mg for IFN-beta-1b. Of the known structural differences between IFN-beta-1a and IFN-beta-1b, only glycosylation affected in vitro activity. Deglycosylation of IFN-beta-1a produced a decrease in total activity that was primarily caused by the formation of an insoluble disulfide-linked IFN precipitate. Deglycosylation also resulted in an increased sensitivity to thermal denaturation. SEC data for IFN-beta-1b revealed large, soluble aggregates that had reduced antiviral activity (approximated at 0.7 x 10(7) IU/mg). Crystallographic data for IFN-beta-1a revealed that the glycan formed H-bonds with the peptide backbone and shielded an uncharged surface from solvent exposure. CONCLUSIONS: Together these results suggest that the greater biological activity of IFN-beta-1a is due to a stabilizing effect of the carbohydrate on structure.

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